REMARKS/ARGUMENTS

Claim Status/Support For Amendments

In response to the Office Action of July 29, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

No new matter has been added by the amendments to the specification.

The Sequence Listing has been replaced with a corrected Substitute Sequence Listing which includes sequence identification numbers for all of the sequences disclosed in the Specification, including the figures.

The title of the application has been amended to more clearly indicate the invention to which the pending claims are drawn.

The Brief Description of the Figures section has been amended to include sequence identification numbers for sequences disclosed in the figures.

Several protocols in the experimental section of the detailed description have been amended to properly identify the trademark SEPHAROSE.

The abstract has been amended to remove the legal phraseology ("said").

Claim 1 has been amended to incorporate the subject matter of canceled claim 2 and to indicate that the claimed biopolymer marker peptide is indeed patentable subject matter. Thus, no new matter

has been added by the amendment to claim 1. Claims 2-38 have been canceled. New claims 39-46 have been added. Claims 1 and 39-46 remain pending in the instant application. Claim 1 (as drawn to a biopolymer marker peptide consisting of amino acid residues 2-14 of SEQ ID NO:1) now constitutes the elected Group I invention, as claim 2, originally included within Group I, has been canceled. As later explained, under the heading **Request for Rejoining of Claims** (see page 11), if the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with *Ochiai* is respectfully requested.

No new matter has been added by the addition of new claims 39-46. The subject matter of new claims 39-46 corresponds with subject matter originally found in cancelled claims 2-38. The above additions to the claims also find basis in the original disclosure at page 25, line 16 to page 26, line 22. The method of new claim 39 is described in detail at pages 37-47. Page 48, lines 5-9 refers to use of various types of samples and page 39, line 3 to page 40, line 12 refers to different mass spectrometric techniques. Page 47, line 5 refers to practicing the claimed methods with a human patient. Pages 47-50 describe kits contemplated for use with the claimed methods. Lines 1-5 on page 48 refer particularly to the immobilizing on solid supports and labeling of components of the contemplated kits. It is clear from these specific recitations and from the description of methods utilized that the methods and types

of kits recited in the newly added claims (39-46) were fully contemplated by the inventors at the time of filing and were enabled by virtue of the disclosure as originally filed.

Request for Rejoining of Claims

The instant application is related in claim format to several pending applications of which serial number 09/846,352 is exemplary. The biopolymer marker of serial number 09/846,352 was found to be novel and subsequently claims reading on methods and kits limited to its use were rejoined with the claims reading on the biopolymer marker under *Ochiai*. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner enter new claims 39-46 in the instant application as being drawn to a non-elected invention and consider joining them (new claims 39-46) with claim 1 of the elected invention (Group 1) upon the Examiner's determination that the claim of the elected invention is allowable, since if the peptide consisting of amino acid residues 2-14 of SEQ ID NO:1 is found to be novel, methods and kits limited to its use should also be found novel.

Sequence Compliance

The specification stands objected to for failing to comply with the requirements of 37 CFR 1.821 through 1.825. Specifically,

the amino acid sequences disclosed in the chart in Figure 2 have not been included in the Sequence Listing filed on February 13, 2002.

Applicants have reviewed the entire specification, including the figures and the claims, for sequence disclosures. The only sequences found to be disclosed are found at page 46 and in Figure 2 of the originally filed specification. Applicants provided a Sequence Listing (in both paper and computer readable form) disclosing the four amino acid sequences on page 46 on February 13, 2002. However, Applicants now note that the amino acid sequences shown in the chart in Figure 2 were not included in the originally filed Sequence Listing. Applicants herein provide a diskette containing a substitute Sequence Listing in electronic computer readable form to replace the previously submitted copy (filed on February 13, 2002). The diskette submitted herewith contains a Sequence Listing which adds the amino acid sequences shown on the chart in Figure 2. Applicants also herein provide a substitute paper copy of the Sequence Listing as contained on the diskette filed herewith. The computer readable form of the substitute Sequence Listing is identical to the paper copy of the substitute Sequence Listing. No new matter has been added as the amino acid sequences on page 46 and in Figure 2 were disclosed in the specification as originally filed.

Additionally, on page 46 of the original disclosure, the first

and last amino acid residues of each of SEQ ID NOS:1-4 are shown in parentheses. When carrying out mass spectrometric procedures, it is possible to fragment a whole molecule, depending upon the enzyme used for digestion. A sequence is often predicted from these fragments but often the sequence is not identified completely. It is conventional in the art to show the missing portions of the predicted sequence in parentheses. The first and last amino acid residues of SEQ ID NOS:1-4 are predicted residues as disclosed by the parentheses on page 46 of the original disclosure. Thus, no new matter is added. The first and last amino acid residues of SEQ ID NOS:1-4 are disclosed in the Sequence Listing, however the biopolymer marker peptide identified from proteins in patient sera consists of amino acid residues 2-14 of SEQ ID NO:1. The amendments to the claims and specification limiting the biopolymer marker peptide sequence to specific amino acid residues are made for the purpose of clarification of the use of parentheses only. The claims as herein amended limit the biopolymer marker peptide sequence to amino acid residues 2-14 of SEQ ID NO:1.

Thus, Applicants respectfully submit that the instant application is now in compliance with 37 CFR 1.821 through 1.825 and request that the above-discussed objection be withdrawn.

Rejection under 35 USC 101

Claims 1 and 2, as originally presented, stand rejected under 35 U.S.C. 101 because the claimed invention allegedly is directed to non-statutory subject matter. The Examiner alleges that the claims fail to include any limitations, which would distinguish the claimed polypeptide sequence from those which occur in nature.

Claim 2 has been canceled and the subject matter of claim 2 has been incorporated into amended claim 1. None of the pending claims recite the term "analyte". Claim 1 has been amended to recite an isolated biopolymer marker. As used within the instant specification (at page 20, lines 9-16), the term "isolated"is interpreted to mean "altered by the hand of man" from its natural state, for example, if it occurs in nature and it is then "isolated", it has been changed or removed from its original environment or both. A polypeptide, such as that claimed herein (amino acid residues 2-14 of SEQ ID NO:1), naturally present in a living organism is not "isolated", however the same polypetide separated from the co-existing materials of its natural state is "isolated". It is clear from the methods recited herein that the claimed polypeptide marker (amino acid residues 2-14 of SEQ ID NO:1)is obtained from samples which have been isolated from a patient's body, thus the claimed polypeptide is "isolated" (see page 46, lines 3-14).

Accordingly, it is respectfully submitted that the Applicants

have now shown that the claimed invention is drawn to patentable subject matter. Thus, Applicants respectfully request that the above-rejection under 35 U.S.C. 101 be withdrawn.

Rejection under 35 USC 112 (second paragraph)

Claims 1 and 2, as originally presented, stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner alleges that claim 1 is vague and indefinite because it is not clear whether "analyte thereof" refers to a biopolymer marker or to SEQ ID NO:1. The Examiner states that according to the instant specification, "biopolymers" are defined as "biological molecules/macromolecules" and an "analyte" is defined as "any atom and/or molecule; including their complexes and fragment ions" (page 6, lines 15-19). The Examiner alleges that the definitions of these two terms appear to be conflicting, because one would not recognize an atom as a biopolymer.

Claim 1 has been amended and does not recite the phrase "analyte thereof". The phrase "analyte thereof" is not recited in any of the remaining pending claims. Furthermore, it is clear from reading amended claim 1 that amino acid residues 2-14 of SEQ ID NO:1 is the biopolymer marker.

Accordingly, applicants have now clarified the metes and

bounds of the claims and respectfully request that the above-discussed rejection under 35 U.S.C. 112, second paragraph be withdrawn.

Rejection under 35 USC 112 (first paragraph)

Claims 1 and 2, as originally presented, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner alleges that the instant specification fails to provide any guidance on how to use the disclosed polypeptide of SEQ ID NO:1 as a marker or indicator of any disease state, including Alzheimers disease. The Examiner further asserts that there is no information disclosed in the instant specification which would provide evidence or sound scientific reasoning that a biopolymer marker (SEQ ID NO:1)is specifically associated with any particular disease state in general or with Alzheimers disease in particular.

Applicants respectfully disagree with the Examiner's assertions. Claim 2 has been canceled and the subject matter has been incorporated into amended claim 1. Claim 1 has been limited to a specific biopolymer marker peptide (amino acid residues 2-14 of SEQ ID NO:1) specifically diagnostic for Alzheimers disease.

Applicants are not required to explain the disease process in Alzheimers disease; applicants are only required to show that the claimed peptide is indicative of Alzheimers disease (see MPEP 2165.03). Applicants respectfully submit that the instant disclosure, including the figures, shows that the claimed peptide is indicative of Alzheimers disease.

Applicants provide a general disclosure of the protocols and methods used to identify the claimed biopolymer marker peptide at pages 37-40 of the instant specification. Pages 40-46 of the instant specification provide specific steps and protocols one would carry out in order to identify the claimed biopolymer marker peptide. Furthermore, electrophoretic, mass spectrometric and chromatographic techniques are well-known to those of skill in the art, thus even if specific protocols were not included within the disclosure, one of skill in the art would be familiar with the techniques used and would know how to carry out the protocols in the instant disclosure. Alternatively, if one of skill in the art did not know exactly how to carry out the protocols of the instant invention, one of skill in the art would know where to locate the information in the prior art since the techniques used in the instant disclosure are well-described in the art. Applicant is not required to describe what is well known in the art. A patent need not teach, and preferably omits, what is well known in the art (see MPEP 2164.01).

Applicants clearly teach in the instant specification how the claimed peptide was determined to be diagnostic for Alzheimers disease and further set forth a method which can be followed to determine markers of any disease condition. For example, according to the method of the instant invention; biological samples (types of samples are listed at page 48, lines 5-9 of the instant specification) are obtained from both patients having a disease condition and healthy (normal) patients. The two groups of samples are resolved by polyacrylamide gel electrophoresis and the resulting protein bands appearing from the samples obtained from patients having a disease condition are compared to protein bands appearing from the samples obtained from healthy (normal) patients. Bands which differ in some way (up-regulated, down-regulated, present and/or absent) between the samples are excised and purified from the gel. The proteins (found in the bands) are subjected to enzymatic digestion, chromatography and identification by mass spectrometric techniques. Thus, none of the bands found in the gels correspond directly to the claimed peptides. The bands represent whole proteins and/or groups of proteins as they are separated from the patient sample. The claimed peptides are fragments of the whole proteins excised from the gel. For example, Figure 1 shows a polyacrylamide gel with three labeled bands (C1, C2 and C3). Lanes 1-10, on Figure 1, as read from the left contains the following samples: Lanes 1-4 contain samples from patients having Alzheimers

disease; Lanes 5-8 contain samples from patients not showing signs of Alzheimers disease who are age-matched to the patients having Alzheimers disease; Lane 9 contains multiple serum samples from healthy (normal) patients of various ages and lane 10 contains the molecular weight standard marker ladder used to interpret molecular weights of protein bands appearing in the lanes. Patient sample numbers are indicated at the bottom of each lane. This gel results from a DEAE 3 protocol shown at page 41 of the instant specification; step 3 clearly indicates that the samples are sera. Bands C1 and C3 appear as strongly expressed as compared with band C2 of corresponding location in different lanes. Bands C1 and C3 appeared in samples from age-matched patients and band C2 appeared in samples from patients having Alzheimers disease. Thus, band C2 can be said to be down-regulated in Alzheimers disease. The three bands (C1, C2 and C3) were excised from the gel and subjected to the above-described protocols. The claimed biopolymer marker peptide was isolated from these bands and identified as a fragment of the complement C3 precursor. Since this protein appears to be down-regulated in Alzheimers disease, it is considered to be indicative of Alzheimers disease. Thus, Applicants respectfully submit that the instant specification provides sufficient guidance on how to identify and use the claimed biopolymer marker peptide as a marker of Alzheimers disease.

There is no conventional control applied in the methods of the

instant invention. Both samples from diseased patients and healthy patients are separated by gel electrophoresis. The protein bands which differ between diseased and healthy samples are excised from the gel. A determination of up-regulation, down-regulation, presence and/or absence of the proteins present in the bands is assessed by sample at the time they appear, for example, as described above, the claimed biopolymer marker peptide was identified as down-regulated in Alzheimers disease.

A Declaration Under 37 CFR 1.132 is submitted herewith in order to clarify the use of controls in the experiments disclosed in the instant specification.

One of skill in the art would recognize from the protocols and figures disclosed in the instant specification that the claimed biopolymer marker peptide is indicative of Alzheimers disease. Thus, Applicants respectfully submit that the instant specification provides sufficient guidance on how to use the claimed biopolymer marker peptide as an indicator of Alzheimers disease.

The Examiner asserts that the specification fails to explain the relationship between a polypeptide of SEQ ID NO:1 and a particular disease state. The Examiner questions "Is the up or down regulation of the marker relative to the categorization of the disease state?" and "Is the presence or absence of the polypeptide of SEQ ID NO:1 indicative of a disease?" The Examiner asserts that the instant specification does not provide answers to these

questions and thus undue experimentation is required to answer these questions. Applicants respectfully disagree with the Examiner's position. Page 5, lines 12-22 (of the instant specification), state that the present inventors do not attempt to develop a reference of "normal" but rather strive to specify particular markers whose presence, absence or relative strength/concentration in disease vs. normal is diagnostic of at least one specific disease state or whose up-regulation or down-regulation is predictive of at least one specific disease state. The relationship is observed from a comparison of disease spectra to normal (healthy) spectra. This is a simple method of analysis that requires identification of differences in the spectra of the disease state versus the spectra of the non-disease state. Such simple analysis does not require "undue experimentation". Thus, the instant specification clearly explains the relationship between the claimed biopolymer marker peptide and Alzheimers disease and further teaches one of skill in the art how to determine if a marker is indicative of any disease state.

The Examiner provides references (Clark *et al.* Archives of Neurology 50:1164-1172 1993 and Motter *et al.* Annals of Neurology 38(4):643-647 1995) which she asserts indicate that it is well-known in the art that a diagnosis of Alzheimers disease is only definitive at postmortem examination or at brain biopsy.

The first thing noted about the references is the publication

dates; each article was published more than five years prior to the date of Applicants' invention. Theories and standards in biotechnology and medicine change quickly over time and especially over a five year period. Thus, these references are not considered to accurately assess the state of the art at the time of the Applicants' invention.

Even if these references were contemporary to the state of the art at the time of the invention, they remain insufficient to support the Examiner's position on the enablement of the instant invention. These references may state that the diagnosis of Alzheimers disease is only definitive at postmortem examination or at brain biopsy; but these references do not state or suggest that these will be the only effective means for the diagnosis of Alzheimers disease ever to be used. The instant invention provides improved alternative means for the diagnosis of Alzheimers disease. It is clear from the experiments described in the specification that the instant inventors have developed a method that can provide a simple alternative to the traditional diagnosis of Alzheimers disease, which when applied can lead to earlier diagnosis and thus more effective treatment and an improvement of the quality of life for patients. Thus, for the reasons discussed in the above two paragraphs, the cited references are not deemed relevant to support the Examiner's position.

The Examiner further asserts that the specification fails to

disclose any specific information regarding the data presented in Figures 1 and 4, such as, description of a sample, the representative number of samples, description of control samples and a method of evaluation of the bands displayed in Figures 1 and 4 which leads to a conclusion that they are indicative of Alzheimers disease. The Examiner additionally asserts that a skilled artisan would have to resort to substantial amounts of undue experimentation to discover how to use the claimed biopolymer marker peptide in prediction of Alzheimers disease; such experimentation including determination if the marker is absent or present or strongly present in a normal individual, or is up-or down-regulated in disease.

Applicants respectfully submit that the assertions of the Examiner presented in the paragraph immediately prior to the instant paragraph were addressed previously at pages 17-20 of the instant Response.

Accordingly, as demonstrated by the discussion presented above, Applicants assert that one of ordinary skill in the art when reviewing the instant specification and declaration filed herewith would recognize how to use the claimed biopolymer marker peptide (amino acid residues 2-14 of SEQ ID NO:1) as a marker for indication of Alzheimers disease. Thus, Applicants respectfully request that this rejection now be withdrawn.

Rejection under 35 USC 102(b)

Claim 1, as originally presented, stands rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Walsh ("Enzymatic Reaction Mechanisms" W.H. Freeman and Company, pages 425-426, 1977).

The Examiner states that claim 1 is directed to a biopolymer marker of SEQ ID NO:1 or at least one analyte thereof useful in indicating at least one particular disease state. An "analyte", according to the instant specification, is defined as "any atom and/or molecule; including their complexes and fragment ions. This term may refer to a single component or a set of components (see page 6, lines 15-17). Thus, claim 1 encompasses a molecular embodiment, the structural feature of which can be an atom, or a molecule, such as an amino acid. The Examiner further states that although claim 1 is not limited to a biopolymer marker consisting of one amino acid, during patent examination, the pending claims must be given their broadest reasonable interpretation consistent with the specification. Therefore, the Examiner alleges that one would reasonably believe that claim 1 encompasses one amino acid, such as phenylalanine (Phe), which is present within SEQ ID NO:1, as an analyte of a biopolymer marker useful in indicating one particular disease. The Examiner alleges that Walsh describes a well-known pathological condition, phenylketonuria, which is characterized by elevated blood and urinary levels of

phenylalanine. Thus, the Examiner alleges that the disclosure of Walsh meets the limitations of claim 1.

Claim 1 has been amended to recite an isolated biopolymer marker peptide consisting of amino acid residues 2-14 of SEQ ID NO:1 diagnostic for Alzheimers disease. The term "analyte" has been removed from the claim. Claim 1, as instantly presented, recites a specific peptide (amino acid residues 2-14 of SEQ ID NO:1) with a specific function (diagnostic for Alzheimers disease). Furthermore, since "consisting of" is closed language and excludes any element, step or ingredient not specified in the claim (see MPEP 2111.03), the scope of the instant claim now encompass only this specific peptide (amino acid residues 2-14 of SEQ ID NO:1) thus excluding the single amino acid phenylalanine as described by Walsh. No where does Walsh teach the claimed peptide (amino acid residues 2-14 of SEQ ID NO:1). Nor does Walsh teach any amino acid or peptide which is diagnostic for Alzheimers disease.

Accordingly, Applicants respectfully submit that the claim, as instantly presented, now distinguishes over the compositions taught by Walsh and respectfully request that this rejection be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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